

Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1, and 6-7 are pending in the application, with claim 1 being the independent claim. Claims 2, 4 and 5 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. Claims 1 and 7 have been amended. Support for the amendment to claim 1 can be found in the specification on pages 7, 8 and page 14, line 27 through page 15, line 2. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Supplemental Information Disclosure Statement

Applicants note that a Second Supplemental Information Disclosure Statement is submitted accompanying the Amendment and Reply. Applicants respectfully request the Examiner initial and return a copy of Information Disclosure Statement Forms.

II. Priority

The Office has requested English language translations of the German language priority documents. Applicants submit herewith certified translations of both priority documents for the instant application.

III. Description of the Invention

The present invention relates to novel active compound combinations comprising, a synergistically effective amount of a compound of formula (I) and at least

one compound of formula (II) wherein the compound of formula (I) and the compound of formula (II) are present in a ratio of from 250:1 to 1:50.

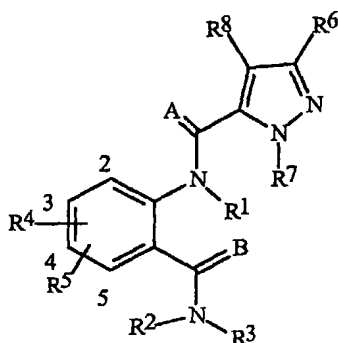
IV. Rejections under 35 U.S.C. § 103(a)

Rejection of claims 1-2, and 4-5 under 35 U.S.C. § 103(a) as allegedly being unpatentable over International Publication No. WO 03/015518 A1, to Lahm *et al.* ("the WO '518 publication"), in view of in view of Ohkawara *et al.*, "Clothianidin: a novel broad-spectrum neonicotinoid insecticide," *British Crop Protection Council Conference-Pests and Diseases*, 1:51-58 (2001) ("Ohkawara"), Blumel and Gross, "Effect of pesticide mixtures on the predatory mite *Phytoseiulus persimilis* A.H. (Acarina, Phytoseiidae) in the laboratory," *J. Appl. Ent.*, 125:201-205 (2002) ("Blumel"), and Colby, "Calculating Synergistic and Antagonistic Responses of Herbicide Combinations," *Weeds* 15:20-22 (1966) ("Colby"), is respectfully traversed. In view of the cancellation of claims 2, 4 and 5, the rejection of claims 2, 4 and 5 is rendered moot.

A. Prima facie Case of Obviousness Has Not Been Established

The Office states that the WO '518 publication discloses a method of controlling pests by administering the elected compound chlorantraniliprole (coragen) and explicitly teaches that chlorantraniliprole can be combined in a mixture with other biologically active agents. Office Action, pp. 7-8. Applicants respectfully disagree and submit that the Office has not established a *prima facie* case of obviousness.

The WO '518 publication is directed to a very broad genus of compounds of formula I as shown below:



wherein R^1 - R^8 may be a large number of substituents. Thus, the WO '518 publication discloses hundreds of thousands of compounds.

The WO '518 publication also generally discloses that compounds of Formula 1 can be mixed with one or more other biologically active compounds or agents, such as insecticides, fungicides, nematocides, bactericides, acaricides, growth regulators, etc. The '518 publication mentions hundreds of such insecticides, fungicides, nematocides, bactericides and acaricides.

The WO '518 publication therefore discloses an infinite number of possible combinations of the anthranilamide compounds of Formula 1 and one or more other biologically active compounds or agents. Even though the WO '518 publication specifically discloses the compound II-1-4, it does not specifically disclose combining the compound II-1-4 with one or more other biologically active compounds or agents. Applicants respectfully disagree with the Offices' statement that "[s]pecifically, the WO '518 publication teaches that coragen can be combined with clothianidin (p. 42, Example 11, p. 141, claims 6 and 9)." Office Action, p. 8. Example 11 on page 42 of the WO '518 publication is a specific disclosure of compound II-1-4 alone. Moreover, claims 6 and 9 of the WO '518 publication are directed to compositions comprising a compound

of formula I along with an additional biologically active compound or agent. The present claims recite a synergistic composition comprising a compound of formula I selected from the group consisting of compounds Ia, Ie, Ig, Ih, Ii, Ik, Il, and Im and a compound of formula II. The Office has not articulated a reason why a person of ordinary skill in the art would combine the compound II-1-4 with clothianidin (compound Im). In addition, present claims recite the mixing ratio of a compound of formula I to a compound of formula II from 250:1 to 1:50. As acknowledged by the Office, the WO '518 publication also does not provide any guidance as to the mixing ratio as recited in present claim 1.

Ohkawara and Blumel do not cure the deficiencies of the WO '518 publication. The Office states that because the WO '518 publication discloses that chlorantraniliprole (coragen) also provided significant plant protection at low levels of application, it would have been obvious to one of ordinary skill in the art to prepare a formulation comprised of both coragen and clothianidin. Office Action, pp. 10-11. Applicants respectfully disagree and submit that the reasoning used by the Office is flawed. Neither the WO '518 publication nor Ohkawara indicate that the claimed compounds may be combined to arrive at a synergistic combination. While Ohkawara discloses the low toxicity of the compound clothianidin, it does not provide any indication that clothianidin may be combined with any other compounds to provide a synergistic composition. Neither does Ohkawara suggest the categories of compounds or any specific compounds that may be combined with clothianidin.

The Office states that the "combined references of the WO '518 publication, Ohkawara *et. al.*, and Blumel *et. al.* teach that the combination of coragen and

clothianidin would have resulted in a potent, synergistic pesticidal formulation." Office Action, p. 12. Applicants respectfully disagree. Blumel does not provide any indication that the claimed compounds can be combined to achieve a synergistic combination. In fact, the compositions tested in Blumel are completely different from the compositions of the instant claims. Therefore, there is nothing in the combined references of the WO '518 publication, Ohkawara, and Blumel that would cause a person of ordinary skill in the art to select the compounds claimed in the present invention, and combine them in a synergistic combination at the ratio specified in the instant claims.

The Office also cites Colby to support the proposition that it would also have been *prima facie* obvious for one of ordinary skill in the art to arrive at the ratio range of 250:1 to 1:50 by routine optimization of the amounts of coragen and clothianidin, from the values determined by Colby's formula. Office Action, p. 12. Applicants respectfully disagree and submit that the Office is mischaracterizing Colby. Colby only indicates a method of calculating synergistic effect. Colby does not teach a method of picking a combination of two or more insecticides from among the several hundred thousand possible combinations of insecticides listed in the WO '518 publication. Colby does not provide a method of predicting synergism, as indicated by the Office. It would therefore not have been obvious to use Colby to arrive at ratios of pesticides that achieve synergistic effects.

Under *KSR International Co. v. Teleflex, Inc.*, 127 S.Ct. 1727, 82 U.S.P.Q. 2d 1385, 1741 (USSC) (2007), "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was independently known in the prior art." Rather, there must be a reason or rationale behind an obviousness

determination and "this analysis should be made explicit." *Id.* Hence, under KSR, the mere fact that the individual elements, i.e., compound (II-1-4), chlorantraniliprole, and clothianidin, were independently known in the art does not render the present claim 1 obvious. The Office is using impermissible hindsight analysis to piece together isolated elements taken from the WO '518 publication's laundry list of mixing partners, and the teachings of Ohkawara, Blumel and Colby, with the aid of Applicants' disclosure to arrive at the presently claimed composition.

In sum, there is nothing in any of the cited references that would have provided a reason for making the composition as recited in the present claim 1. Accordingly, the Examiner has not established a *prima facie* case obviousness of claim 1.

B. Unexpected Results Rebut Any Prima Facie Case of Obviousness

As discussed above, the WO '518 publication does not specifically disclose combining the compound II-1-4 with the claimed mixing partners. There is also nothing in Ohkawara and Blumel to aid in the selection of the claimed compounds in a synergistic combination at the ratios defined in the instant claims. Further, Colby does not provide a method for optimizing the ratios of the two compounds.

Even assuming that a *prima facie* case of obviousness has been established, which it has not, the unexpected insecticidal action exhibited by the claimed compounds is sufficient to overcome any *prima facie* case of obviousness. Applicants submit herewith a Declaration under 37 C.F.R. § 1.132 ("Declaration") which recites the unexpected superiority of the claimed invention over WO '518 publication.

In the Declaration, Dr. Wolfram Andersch, an inventor of the present application, recites data from test applications of combinations of compounds according to the present claims and compares it to the compounds applied alone. In the study, either cabbage leaves (*Brassica oleracea*) or bean plants (*Phaseolus vulgaris*) heavily infested with four different insects were sprayed with a preparation of the active compound at the desired concentration. After the specified period of time, mortality in % was determined.

Results Presented in the Declaration

(a) *Myzus persicae* test

In the study described in Example A of the Declaration, cabbage leaves that were infested by *Myzus persicae* were sprayed with preparations of tested compounds individually, or with preparations of the claimed compositions. The efficacy of insect control was evaluated after specified days of the treatment (*e.g.*, 1 day or 6 days after the treatment). (Declaration, Example A and Tables A1 - A4.)

As shown in Table A1, when the anthranilamide compound and compound 1k are applied individually at a concentrations of 0.0064 gram per hectare and 0.16 gram per hectare, respectively, each exhibits an efficacy of 0%. However, an efficacy of 50% was observed when the claimed composition at the specified ratio of 1:25 (0.0064:0.16) was applied. Thus, the efficacy of the claimed composition was *much greater than* not only the sum of the efficacies (0%), but also greater than the efficacy calculated by the Colby formula. Similar results were seen in Table A2, where efficacies of compounds were evaluated after 6 days of application. All of the anthranilamide compounds and compound 1k exhibited an efficacy of 0% at an when applied individually at an

application rate of 0.0064 and 0.16 grams per hectare, respectively. However, in combination, each of the compositions exhibited an efficacy *significantly higher than* the individual efficacies. Tables A3 and A4 also demonstrate the efficacies of the combinations of II-1-9, II-1-54, II-1-52, II-1-1, II-1-12 and II-1-4 with compounds Im, Ia and Ik, at 1 and 6 days after application, respectively. Firstly, most of the compounds of formula II demonstrate 0% efficacy after individual application. Secondly, upon application in combination with compounds of formula I, the observed efficacy is not only much higher than the sum of the individual efficacies, but also higher than the calculated efficacy of the combination according to the Colby formula.

(b) *Phaedon cochleariae* Test

Example B of the Declaration evaluated the killing efficacy of the larvae of the mustard beetle (*Phaedon cochleariae*) with compositions according to claim 1 in comparison with compounds of formula I and II applied individually. Table B1 and B2 evaluated four compounds of formula II and two compounds of formula I, individually and in combination at 2 and 6 days respectively. The compounds in combination were at a ratio according to the present claims. Each of the combinations exhibits an efficacy much greater than the efficacy of the individual compounds. For example, compound II-1-2 and compound Ia in combination at concentrations of 0.8 and 20 grams per hectare (1:25), respectively, exhibit an efficacy of 100% after 2 days, while exhibiting an individual efficacies of 0% and 17%, individually at the same concentrations.

(c) *Spodoptera frugiperda* Test

In the study described in Example C of the Declaration, cabbage leaves were first sprayed with preparations of tested compounds individually, or with preparations of the

claimed compositions. The cabbage leaves were then infested with larvae of the fall army worm (*Spodoptera frugiperda*). The efficacy of insect control was evaluated after specified days of the treatment (2 or 6 days after the treatment). (Declaration, Example C and Tables C1 - C4.)

As an example, in Table C2, compounds Im (clothianidin) and Ia both exhibit an efficacy of 0% after 6 days. However, a combination of compound Im and Ia with two different compounds of formula II exhibits efficacies much higher than the calculated combined efficacy. Table C3 demonstrates the efficacies of combinations of compounds II-1-54, II-1-52, II-1-1 and II-1-12 with compounds Im, Ia and Ik, at a ratio according to the present claims after 2 days of application. As an example, a combination of compound II-1-54 with Im at a ratio of 1:1 exhibits an efficacy of 33% after two days, which is much higher than the calculated efficacy of 0%. A combination of compound II-1-24 with Ia at a ratio of 1:25 exhibits an efficacy of 100% after two days, which is much higher than the calculated efficacy of 50%. (Table C4.)

(d) *Tetranychus urticae* Test

In the study described in Example D of the Declaration, bean plants (*Phaseolus vulgaris*) heavily infested with all stages of the two-spotted spider mite (*Tetranychus urticae*) were treated by being sprayed with preparations of the active compounds, either individually, or in combination, and efficacy (insect mortality) determined after 2 or 6 days. (Table D1 and D2.)

Compounds of formula II (II-1-54, II-1-52, II-1-24 and II-1-4) and compound Im exhibited a zero to 20% efficacy upon individual application. However, in combination, at a ratio according to the instant claims, the observed efficacy was significantly higher.

For example, in Table D1, a combination of compound II-1-24 (at 100 g/ha) and compound Im (at 10 g/ha) yielded an observed efficacy of 80% mortality after 2 days, which was much higher than the calculated efficacy of 0%. In Table D2, a combination of compound II-1-54 (at 20 g/ha) and compound Im (at 2 g/ha), exhibited an observed efficacy of 40%, when compared to a calculated efficacy of 0%, and compounds II-1-54 (at 20 g/ha) in combination with compound Ik (at 2 g/ha) exhibited an efficacy of 60%, compared to a calculated efficacy of 0%.

Therefore, the unexpected results present in the Declaration rebut any *prima facie* case of obviousness of the present claims in view of the WO '518 publication, Ohkawara, Blumel and Colby. Applicants respectfully request that this rejection be withdrawn.

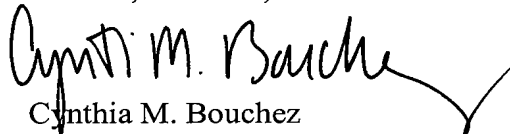
Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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